



REVIEW

Antibiotic therapeutic options for infections caused by drug-resistant Gram-positive cocci

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Summary Serious infections caused by Gram-positive bacteria are currently difficult to treat because many of these pathogens are now resistant to standard antimicrobial agents. As a result of the emergence and spread of multidrug-resistant Gram-positive pathogens, new antimicrobial agents are urgently needed for clinical use. In recent years, there has been an increase in the number of drugs that have activity against these Gram-positive pathogens. Daptomycin, tigecycline, linezolid, quinupristin/dalfopristin and dalbavancin are five antimicrobial agents that are useful for the treatment of infections due to drug-resistant Gram-positive cocci. This review focuses on their mechanism of action, pharmacokinetics, spectrum of activity, clinical effectiveness, drug interaction and safety. These antimicrobial agents provide the clinician with additional treatment options among the limited therapies for resistant Gram-positive bacterial infection.

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Contents

Introduction.....	63
Daptomycin.....	63
Clinical trials.....	65
Safety profile.....	65
Tigecycline.....	66

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Clinical trials.....	66
Safety profile.....	67
Linezolid.....	67
Clinical trials.....	67
Safety profiles.....	68
Quinupristin–dalbavancin.....	68
Clinical trials.....	69
Safety profile.....	69
Dalbavancin.....	69
Clinical trials.....	70
Safety profile.....	70
Other emerging antibiotics.....	70
Conclusion.....	70
Conflict of interest.....	70
References.....	71

Introduction

Serious infections caused by Gram-positive bacteria continue to pose significant treatment challenges. These difficult-to-treat pathogens which include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), vancomycin intermediate and resistant *S. aureus* (VISA and VRSA), coagulase-negative staphylococci (CoNS) and penicillin-resistant *Streptococcus pneumoniae* (PRSP) have assumed world-wide notoriety with associated increasing morbidity and mortality [1,2]. Hence, there is an urgent need for effective novel antibiotics which not only target these pathogens but also possess suitable pharmacokinetic properties and safety profiles. In recent years, we have witnessed significant advances in drug development which have resulted in the introduction of new antibiotics into the armamentarium available to clinicians. This review presents an analysis of five new generation antibiotics (daptomycin, tigecycline, linezolid, quinupristin/dalbavancin) some of which are currently in use in clinical settings. The dosages, route of administration and side-effects of the drugs are shown in Table 1.

Daptomycin

This new semi-synthetic cyclic lipopeptide was approved by the Food and Drug Administration (FDA) in 2003 for the treatment of complicated skin and soft tissue infections (cSSI) caused by susceptible Gram-positive pathogens and European approval was granted in January 2006 [3]. Its chemical structure is composed of a 13-amino acid cyclic peptide with a hydrophilic core and a lipophilic tail [4]. The short peptide chains conjugated with an

acyl chain form a structurally defined conformation which is responsible for the unique mechanism of action of daptomycin. The insertion of the lipophilic tail into the bacterial membrane results in the formation of pores with leakage of cellular material, dissipation of the transmembrane potential as well as widespread disruption of macromolecular synthesis ultimately culminating in a rapid bactericidal effect [5].

In vitro and *in vivo* studies have demonstrated that daptomycin is effective in a concentration-dependent manner, has a long half-life (8 h) and demonstrates a prolonged post-antibiotic effect of up to 6.8 h, hence the recommendation is for a once daily dosing [6,7]. Due to its poor absorption via the gastrointestinal tract, parenteral administration is necessary to achieve adequate serum concentration. Daptomycin is highly bound to serum proteins and is primarily distributed in the extracellular fluid with penetration to vascular tissues [3,8,9]. However, it fails to cross the blood–brain barrier or penetrate the cerebrospinal fluid of normal individuals. Additionally, animal studies have demonstrated poor penetration of daptomycin into the alveolar lining [10]. Drug elimination occurs through the renal mechanism and it is excreted largely unchanged in the urine. The normal 8 h half-life of daptomycin increases to as high as 30 h when there is renal impairment, hence dose adjustment is mandatory for patients with renal failure [11]. As daptomycin does not induce or inhibit the activities of cytochrome P450 or other hepatic enzymes and because of its unique mechanism of action, no antagonistic drug interactions have been observed [12].

Daptomycin's antimicrobial effect is directed against Gram-positive bacteria including multidrug-resistant strains [13,14]. Its spectrum of activity encompasses methicillin-sensitive *Staphylo-*

Table 1 Characteristics of newer antimicrobial agents used in the therapy of infections caused by drug-resistant Gram- positive cocci.

Drug	Route	Dosage	Indications	Adverse effects
Daptomycin	IV	4 mg/kg/day for cSSI; 6 mg/kg/day for bacteremia	1. Complicated skin and skin structure infections (cSSSI) caused by methicillin-sensitive <i>Staphylococcus aureus</i> (MSSA), methicillin-resistant <i>S. aureus</i> (MRSA), <i>Streptococcus. pyogenes</i> , <i>S. agalactiae</i> , <i>S. dysgalactiae</i> and <i>Enterococcus faecalis</i> ^a . 2. Bacteremia/right-sided infective endocarditic caused by MSSA and MRSA ^a	Clinical: constipation, nausea and headache; laboratory: increased creatinine phosphokinase [8,9]
Tigecycline	IV	Loading dose of 100 mg, followed by a maintenance dose of 50 mg every 12 h	1. Complicated intra-abdominal infections including MRSA in adults ^a . 2. cSSSI including MRSA in adults ^a	Clinical: nausea, vomiting, diarrhoea, headache, hypertension and fever [35,36]
Linezolid	Oral or IV	600 mg orally/IV every 12 h	1. Nosocomial and community-acquired pneumonia ^a . 2. Uncomplicated and complicated skin infections ^a . 3. Vancomycin-resistant <i>Enterococcus faecium</i> (VREF) including cases with bacteremia ^a	Clinical: diarrhoea, headache, nausea and vomiting; laboratory: thrombocytopenia [56]
Quinupristin/dalfopristin	IV	7.5 mg/kg every 8 h	1. Serious infections associated with VREF ^a . 2. cSSI caused by MSSA and <i>S. pyogenes</i> ^a	Clinical: arthralgia, myalgia, nausea, vomiting, rash, pain and pruritus; laboratory: hyperbilirubinemia and elevated liver enzymes [68]
Dalbavancin	IV	1000 mg on day 1 and 500 mg on day 8	1. Skin and soft-tissue infections. 2. Catheter-related bloodstream infections caused by Gram-positive pathogens (including MRSA)	Clinical: oral candidiasis, diarrhoea, constipation and febrile response [74,75]

^a Approved by The U.S. Food and Drug Administration (FDA).

coccus aureus (MSSA), methicillin-resistant *S. aureus* (MRSA), vancomycin-intermediate resistant *S. aureus* (VISA), vancomycin-resistant *Enterococcus faecalis* and *E. faecium* (VRE), coagulase-negative staphylococci (CNS), streptococci (*S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae* subsp. *Equimilis*) and penicillin-resistant *S. pneumoniae* (PRSP) [7]. It is also of interest that *in vitro* activity has been demonstrated against the recently isolated Michigan and Pennsylvania (Hershey) strains of vancomycin-resistant *S. aureus* with minimum inhibitory concentrations (MICs) of 1.0 and 0.5 mg/L, respectively [9]. Additionally, daptomycin has been shown to have potent antimicrobial activity against *Corynebacterium* spp. and a variety of anaerobic species [15,16].

Clinical trials

The vast majority of daptomycin clinical trials have been in patients with complicated skin and skin structure infections (cSSSI), *S. aureus* bacteremia and right-sided endocarditis, urinary tract infections (UTI) and pneumonia. In 2004, Arbeit et al. [17], reported the findings of two international Phase 3 multicenter, randomized, controlled, evaluator-blinded trials comparing the safety and efficacy of daptomycin with that of conventional therapy for the treatment of patients with cSSSI requiring hospitalization. In both trials patients were randomized to receive either daptomycin administered at 4 mg/kg intravenously (iv) qd by 30 min infusion or comparator regimen comprising of either cloxacillin, nafcillin, oxacillin or flucloxacillin (4–12 g iv qd in equally divided doses), or vancomycin, 1 g iv q12h by 60 min infusion. The findings of both trials clearly demonstrated that the efficacy of daptomycin therapy was not inferior to that of comparator therapy [17]. Across both studies ~83% of the patients were clinically evaluable and the success rate in this population was 83.4% and 84.2% (95% confidence interval [CI], –4.0 to 5.6) for daptomycin- and comparator-agent treated patients, respectively. Indeed, similar findings were still demonstrable with analysis of the combined intention to treat population with success rates of 71.5% and 71.1% (95% CI, –5.8 to 5.0) for daptomycin- and comparator-agent treated arms, respectively. Among patients successfully treated with iv daptomycin, a significantly shorter duration of therapy was observed with 63% requiring 47 days of therapy, compared with 33% of comparator-treated patients ($p < 0.0001$). Additionally, on evaluation 3–4 weeks post-treatment, the daptomycin treated patients tended to have a low incidence of relapsing or recurrent infection. The

overall clinical success rates observed in these trials are comparable with those reported for other antimicrobial agents approved for the treatment of cSSSIs including quinupristin–dalfopristin thus validating daptomycin's usefulness in the treatment of cSSSIs.

The efficacy of daptomycin versus standard therapy in staphylococcal bacteremia was evaluated in a recently reported international, multicenter, randomized, controlled open-label phase 3 study [18]. Patients with *S. aureus* bacteremia with or without endocarditis were randomized to receive either iv daptomycin 6 mg/kg body weight or standard regimen of initial low-dose gentamicin plus either an antistaphylococcal penicillin or vancomycin. The primary efficacy end point was treatment success 42 days after the end of therapy. The reported findings indicate that daptomycin is not inferior to standard therapy for *S. aureus* bacteremia and right-sided endocarditis. The clinical success rate for daptomycin treated patients was 44.2% (53/120) compared to 41.7% (48/115) for patients who received standard therapy. The pathogen eradication rate was higher for daptomycin compared to standard therapy (19 versus 11 patients, $p = 0.17$). In addition, adverse events resulting in the discontinuation of therapy were significantly higher among patients receiving the standard therapy (17 versus 8, $p = 0.06$). As the efficacy of daptomycin is comparative to standard antibiotic regimen with the added advantage of fewer adverse events, this antibiotic therefore represents a new treatment option for *S. aureus* bloodstream infections. Along a similar trend, daptomycin and ciprofloxacin have been shown to have similar efficacy against Gram-positive organisms (mostly *E. faecalis* and *S. aureus*) for the treatment of complicated UTI [19].

A contrasting finding has been reported for the use of daptomycin in the treatment of pneumonia. In Phase 2 clinical trials, daptomycin (4 mg/kg every 24 h) was compared against ceftriaxone (2 g every 24 h) for the treatment of hospitalized patients with community-acquired pneumonia. The findings indicate that daptomycin which showed clinical efficacy in 79% of subjects was significantly inferior to ceftriaxone (87% efficacy). Subsequent studies using animal models indicate that daptomycin appears to interact *in vitro* with pulmonary surfactant, resulting in inhibition of antibacterial activity [20].

Safety profile

The safety profile of any new antibiotic is relevant to its use in clinical practice. In several clinical studies of daptomycin therapy in adults,

the most common adverse effects reported include diarrhoea, rash, dizziness, dyspnoea and hypotension [3,5,17]. Other adverse events include skeletal muscle symptoms and elevated levels of creatine phosphokinase (CPK). Although the latter has been reported in just about 3% of drug-treated patients, it is still recommended that CPK levels be checked weekly in adults receiving daptomycin therapy. Daptomycin-associated myopathy is mild, reversible and dose dependent and can easily be recognized and confirmed by measuring the CPK levels [21].

Tigecycline

Tigecycline is the first member of a new class of antibiotics called glycylcyclines [22]. The glycylcyclines are derivatives of the tetracycline antibiotics with structural modifications which confer potent activity against Gram-positive, Gram-negative and anaerobic bacteria including multidrug-resistant strains [23]. Tigecycline is a structural analogue of minocycline designed to overcome the major bacterial resistance mechanisms such as efflux pumps, target site modifications, DNA gyrase mutations and beta-lactamase production. It consists of a central four-ring carbocyclic skeleton with a substitution at the D-9 position which confers expanded broad-spectrum activity and decreased susceptibility antibiotic resistance mechanisms [24,25]. By binding reversibly to the 30S ribosomal subunit, tigecycline interrupts the process of protein translation via inhibition of entry of amino-acyl transfer RNA (t-RNA) molecules thus producing a bacteriostatic effect [26]. Additionally, tigecycline uniquely binds to other sites of the ribosome, interfering with the mechanism of production of ribosomal proteins. Indeed, the ribosomal binding affinity of tigecycline has been shown to be up to five times greater than that of the tetracyclines [27,28].

Similar to daptomycin, tigecycline is poorly absorbed following oral administration hence this antibiotic is only available as an intravenous preparation. It is administered by slow iv infusion, 100 mg stat, followed by 50 mg 12 hourly. Over two thirds of the drug is bound to serum proteins and with a high volume of distribution of about 7–10 L/kg, tigecycline is extensively distributed into the tissues [26,29]. It has been shown that following a single 100 mg dose of iv tigecycline considerably higher tissue/fluid drug concentrations is demonstrable in the bile, gallbladder, colon and lung compared with simultaneous serum concentrations [29]. Tigecycline is not extensively metabolized, thus it is largely eliminated unchanged via the biliary (60%)

and renal (22%) mechanisms [26]. Although it has a long half-life of 36 h, in moderate to severe hepatic impairment systemic clearance of the drug is reduced by 25–53% resulting in a 23–43% increment in the elimination of half-life. Thus, reduced dosing regimen of 25 mg 12 hourly is recommended for patients with significant hepatic impairment [26].

Tigecycline is a broad-spectrum antibiotic with potent activity against many Gram-positive and Gram-negative bacteria including many multidrug-resistant strains such as MRSA, MRSE, PRSP and VRE species as well as ESBL-producing *Escherichia coli* and *Klebsiella* spp. [30,31]. Additionally, it has been shown to be effective against *Acinetobacter baumannii*, *Enterobacter* spp., *Serratia marcescens* and *Stenotrophomonas maltophilia* isolates [32]. However, it does not exhibit activity against *Pseudomonas aeruginosa* and *Proteus* spp. Due to its potent microbiological and excellent therapeutic response as reported in phase 3 human clinical trials, tigecycline has received FDA approval for the treatment of infections of skin and skin structures, as well as intra-abdominal infections. Emerging data also indicate its potential use for the empirical treatment of nosocomial and community-acquired infections, including those caused by resistant pathogens [32,33].

Clinical trials

The clinical effectiveness of tigecycline has been studied in patients with cSSSI, complicated intra-abdominal infections (cIAI), UTIs as well as community- and hospital-acquired pneumonia. In two large phase 3 studies, 1116 cSSSI patients were randomized to receive either tigecycline (100 mg stat, followed by 50 mg iv 12 hourly) or comparator regimen of iv vancomycin 1 g twice daily (bid) plus iv aztreonam 2 g bid for up to 14 days [34]. Clinical success rates (intention to treat analysis) in the tigecycline arm were 79.7% (95% CI, 76.1–83.1%) versus 81.9% (95% CI, 78.3–85.1%) ($p=0.42$) for vancomycin–aztreonam therapy. In addition, rates of occurrence of adverse events were similar in both treatment groups. The conclusion from this pooled analysis was that tigecycline monotherapy is of comparative efficacy and safety profile to vancomycin–aztreonam combination in the management of cSSSI [34].

In 2005, Babinchak et al. [35] reported the pooled analysis of two large prospective, double-blind, phase 3 trials, which evaluated the efficacy and safety of tigecycline compared with imipenem–cilastatin in the treatment of patients with cIAI. In both trials patients were randomly assigned to receive either iv tigecycline

(100 mg, followed by 50 mg given bid) or iv imipenem/cilastatin 500/500 mg given every 6 h for 14 days [36]. The findings indicated clinical cure rates of 80.2% for tigecycline in the microbiological modified intent-to-treat population, versus 81.5% for imipenem–cilastatin with similar trends in adverse events in both treatment arms. These findings confirmed the efficacy and safety of tigecycline in the treatment of cIAI [35]. In a recent report, analysis of data from these trials using multiple regression models also demonstrated that tigecycline was similar to imipenem–cilastatin in terms of health resource utilization including duration of iv antibiotic therapy and length of hospital stay [37]. Tigecycline has been shown to be effective against isolates obtained from patients with community- and hospital-acquired pneumonias [32]. Recent data from a double-blind randomized phase 3 comparison study of intravenous tigecycline and levofloxacin in treatment of community-acquired pneumonia demonstrated comparable cure rates for both drugs [38]. However, occurrence of nausea and vomiting was significantly higher in the tigecycline treated patients.

Safety profile

Tigecycline is not an inducer of the CY P450 system and it has been shown to be relatively safe with the most frequently reported adverse events being nausea, vomiting and diarrhoea [22]. The drug interactions of tigecycline are similar to those of tetracyclines. The concurrent use of tigecycline with oral contraceptives may reduce contraceptive efficacy. For patients taking warfarin, prothrombin times or other anticoagulation parameter should be monitored as tigecycline is capable of decreasing the clearance of warfarin by 23–40% and can also increase the peak plasma concentration of warfarin.

Linezolid

This oxazolidinone drug was originally developed as a monoamine oxidase inhibitor for the treatment of depression and its antimicrobial property was a chance discovery [39]. Linezolid inhibits bacterial ribosomal protein synthesis. However, the mechanism by which it achieves this is unique as it targets the first step in protein synthesis by binding to the 50S ribosomal subunit close to its interface with the 30S unit causing distortion of the tRNA binding site. This prevents formation of a 70S initiation complex, which includes fMet transfer RNA, messenger RNA and the two ribosomal subunits [39–41]. As

this mechanism of action is different from that seen in other inhibitors of protein synthesis such as aminoglycosides, macrolides and tetracyclines, occurrence of cross-resistance is avoided.

Linezolid is rapidly and completely absorbed after oral administration with peak plasma concentrations reached within 1–2 h with 100% bioavailability. Approximately one third of the drug is bound to serum proteins and the volume of distribution at the steady state is 40–50 L with a half-life of 4.5–5.5 h after a single oral or iv dose [42]. It is extensively distributed into skin, soft tissue, lung, heart, intestine, liver, urine, kidney and cerebrospinal fluid (CSF). Additionally, fairly good tissue penetration as well as adequate penetration into the synovial fluid, bone, gallbladder and bile is achieved. It is metabolized primarily by slow non-enzymatic oxidation to inactive carboxylic acid derivatives and it does not induce or inhibit the activities of the CY P450. Elimination occurs largely via non-renal mechanism (65%) with renal and fecal mechanisms accounting for 30% and 5%, respectively [39,42]. Available data indicates that dosage adjustment in mild/moderate renal impairment is not required, although it might be necessary in patients with severe renal insufficiency or end-stage renal disease undergoing haemodialysis [43].

Linezolid has bacteriostatic activity against many important pathogens including most Gram-positive species [44–46]. It is active against MSSA and MRSA, as well as glycopeptide-susceptible or resistant enterococci (both Van A and Van B phenotypes), PRSP and erythromycin-resistant pneumococci, Viridans streptococci, erythromycin-resistant *S. pyogenes* and *S. agalactiae*. It is also active against anaerobes including *Clostridium perfringens*, *C. difficile*, *Peptostreptococcus* spp., *Bacteroides fragilis*, *Fusobacterium nucleatum* and *F. meningosepticum* [47]. Although there are no clinical trials on the efficacy of linezolid therapy for central nervous system infections, pharmacokinetics and clinical data in neurosurgical patients indicate the potential efficacy of the drug in the treatment of nosocomial Gram-positive CNS infections including those caused by *Nocardia* spp. [48,49]. Anecdotal case reports indicate a favourable outcome with the use of linezolid in meningitis caused by Gram-positive bacteria including MSSA, MRSA and PRSP.

Clinical trials

To date, the clinical effectiveness of linezolid has only been studied in patients with cSSSI, nosocomial pneumonia, community-acquired pneumonia and infections due to MRSA and VRE [50]. In skin

and soft tissue infections, the efficacy of linezolid has been evaluated in several multinational trials. In a large phase 3 clinical trial, 826 patients with cSSSI were randomized to receive either linezolid 600 mg iv 12 hourly or iv oxacillin 2 g 6 hourly [51]. Clinical success rates were observed in 88.6% and 85.8% for linezolid and oxacillin, respectively. Similar trend for microbiological success rates was observed (linezolid 88.1% versus Oxacillin 86.1%). In another multicenter multinational trial comparing linezolid versus vancomycin for the treatment of cSSSIs, the intention-to-treat analysis of the study population showed that 92.2% and 88.5% of patients treated with linezolid and vancomycin, respectively were clinically cured at the test-of-cure visit [52]. Furthermore, sub-analysis of those with cSSSI due to MRSA showed significantly shorter hospital stay, decreased treatment duration and higher discharge rates for the linezolid arm [53]. These findings indicate that the efficacy of linezolid is equivalent to that of vancomycin for the treatment of cSSSI and where MRSA is the aetiological agent, linezolid is superior to vancomycin. In other reported work, where the efficacy of linezolid for MRSA infections was evaluated in a randomized open-label trial comparing linezolid (600 mg, 12 hourly) with iv vancomycin (1 g, 12 hourly) [54], no statistically significant differences in clinical and microbiological success rates were observed.

In another multinational, randomized, double-blind, controlled trial, linezolid was compared with vancomycin in patients with nosocomial pneumonia [55]. Both treatment arms also received aztreonam. Clinical success rate was documented in 55.6% (115/207) in the linezolid arm and 68.1% (62/91) in the vancomycin arm. Similar microbiological success rates were observed in both treatment groups (linezolid, 67.9% versus vancomycin, 71.8%). These findings confirmed the effectiveness of linezolid for the treatment of Gram-positive nosocomial pneumonia in adults.

Safety profiles

Linezolid is generally well tolerated. Based on data collected on patients in phase 3 clinical trials, the most common adverse effects were diarrhoea, nausea and headache. Serious adverse events like thrombocytopenia, abnormal liver tests and pancreatitis also occurred in some patients [56]. Peripheral neuropathy and optic neuropathy have also been reported in a small number of patients receiving linezolid [57]. As linezolid potentially causes dose- and time-dependent reversible myelosuppression, weekly monitoring of blood counts is necessary particularly with therapy of up to

2 weeks duration [39,58]. Because linezolid is a mild, reversible, nonselective monoamine oxidase (MAO) inhibitor, the potential for interaction with adrenergic or serotonergic drugs and with foods containing large amount of tyramine exists. Therefore, because of the risk of serotonin syndrome, administration of linezolid for patients receiving serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors should be avoided. However, available data [42] indicates that co-administration of linezolid with adrenergic agents resulted in increases in blood pressure but these were within levels associated with normal daily activities.

Quinupristin–dalfopristin

This antibiotic is a combination of quinupristin (type B streptogramin) and dalfopristin (type A streptogramin) at a ratio of 30:70, respectively. Although these two streptogramins which are structurally distinct cyclic peptide antibiotics have a bacteriostatic effect individually, when combined in the appropriate ratio, they have a synergistic bactericidal effect [59]. The two components bind to different sites on the bacterial 50S ribosome leading to inhibition of protein synthesis [60]. Dalfopristin blocks an early step in protein synthesis, whereas quinupristin blocks a later step preventing peptide extension.

Quinupristin–dalfopristin is poorly absorbed after oral administration and thus it is given as an intravenous infusion. The maximum concentration (C_{\max}) ranges from 0.95 mg/L to 24.2 mg/L with a linear relationship between dose and C_{\max} . Maximum tissue concentration is usually achieved within 24 h of administration with excellent penetration into the liver, kidney, spleen, blood, bone marrow, salivary glands, adrenals and the intestinal contents. Protein binding is approximately 11% for quinupristin and 26% for dalfopristin. Both quinupristin and dalfopristin are metabolized to several active metabolites which contribute to the antimicrobial activity [61]. Elimination of the main compounds and their active metabolites occurs largely through hepatic clearance and fecal (biliary) elimination [62].

This combination is effective against a range of Gram-positive organisms that are usually resistant to other agents, including *E. faecium*, *S. aureus* and *S. pneumoniae* [63,64]. Excellent *in vitro* activity with an MIC of $<1 \mu\text{g/ml}$ has been demonstrated in up to 90% of strains of multidrug-resistant Gram-positive organisms, including MSSA, MRSA, coagulase-negative staphy-

lococci (CNS), penicillin-susceptible and -resistant *S. pneumoniae*, *S. pyogenes*, *S. oralis* and *E. faecium* [65,66]. However, strains of *E. faecalis* tend to be resistant to quinupristin–dalbavancin. This drug also shows activity against *Mycoplasma* spp., *Haemophilus influenzae*, *Legionella* spp. and anaerobes (*Clostridium* spp. excluding *C. difficile*, *Peptococcus* spp. and *Peptostreptococcus* spp.) [66]. It is approved for the treatment of infections caused by susceptible strains of vancomycin-resistant *E. faecium* (VREF) and for the treatment of cSSSI caused by methicillin-susceptible *S. aureus* or *S. pyogenes* in adults.

Clinical trials

Two large randomized, open-labelled clinical trials have been conducted in patients ($n=893$) with complicated Gram-positive cSSSI [67]. The studies compared quinupristin–dalbavancin with cefazolin, oxacillin and vancomycin. The clinical success rate was 68% for the quinupristin–dalbavancin group versus 71%, for the comparator regimen. This indicates that, quinupristin–dalbavancin represents an effective alternative for the treatment of cSSSI caused by susceptible Gram-positive organisms. In another large study, patients with bacteremia of unknown origin, bone and joint infection, catheter-related bacteremia, intra-abdominal infection, cSSSI and UTIs [68] were treated using iv quinupristin–dalbavancin, 7.5 mg/kg administered iv every 8 h. The clinical success rate was 74% (95% CI 67–80%) and the bacteriologic success rate was 71% (95% CI 65–78%). The overall clinical and bacteriologic success rate was 66%. However, superinfection by Gram-positive organisms was documented in 22% of patients.

The efficacy of quinupristin–dalbavancin in nosocomial pneumonia was evaluated in a large phase 3 prospective, randomized study conducted in several countries in which it was compared (with or without aztreonam) to vancomycin [69]. A total of 298 patients were enrolled in the study. In the bacteriologically evaluable patients, therapy was clinically successful (i.e., cure or improvement) in 49 (56%) of the 87 patients who received quinupristin–dalbavancin and 49 (58%) of 84 patients who were given vancomycin.

Safety profile

The most commonly reported adverse effects were arthralgias and/or myalgias [69,70]. Laboratory abnormalities were uncommon, but elevated levels of bilirubin and transaminases have been reported. The most frequently reported side effects

attributed to quinupristin–dalbavancin in the clinical studies were muscle and joint pain, nausea, diarrhoea, vomiting and rash. In studies in which the drug was administered through a peripheral vein (e.g. in the arm), many patients experienced local reactions to the injection, including pain and inflammation at the catheter injection site. Quinupristin–dalbavancin has many drug interactions due to its ability to inhibit the metabolism of drugs metabolized by the cytochrome P450 [62].

Dalbavancin

This is a new semi-synthetic second generation lipoglycopeptide antibiotic designed as an improvement on the currently available natural glycopeptides (vancomycin and teicoplanin). It exerts its bactericidal activity by binding to the terminal D-alanyl-D-alanine moiety of the peptidoglycan precursors which results in the blockage of enzymes involved in the final stages of peptidoglycan synthesis and cell wall formation [71]. Although this is the same mechanism seen in the other glycopeptides, dalbavancin is much more potent than vancomycin and teicoplanin. Hence it has been postulated that dalbavancin exerts its bactericidal effect on bacteria through more than one mechanism [72]. It has been suggested that dalbavancin may inhibit transglycosylases, such as *S. aureus* penicillin-binding protein 2 (PBP2), by direct interaction with enzymes involved in the final stages of peptidoglycan synthesis [73].

Dalbavancin is poorly absorbed after oral administration hence parenteral administration is recommended [74]. This drug penetrates well into a variety of bodily tissues and fluids with about 95% bound to plasma proteins [71]. Perhaps the most remarkable pharmacokinetic characteristic of dalbavancin is its long terminal half-life [74]. Following single and multiple doses, the reported terminal half-life of dalbavancin is 149–188 h and 184–198 h, respectively. This long half-life is likely to be due to the extensive protein-binding of the agent which allows prolonged dosing intervals, that can be once weekly for some indications. After intravenous administration of dalbavancin, 35% of the dose is excreted unchanged in the urine [71].

While the spectrum of activity of dalbavancin is similar to the other glycopeptides, it has the advantage of exhibiting superior *in vitro* activity over vancomycin or teicoplanin against susceptible and multidrug-resistant pathogens, including *S. aureus*, CoNS, *S. pyogenes*, *S. pneumoniae*, most

enterococci (except VanA phenotype), *Corynebacterium* spp. and Gram-positive anaerobes [71]. It has potent antimicrobial activity against resistant Gram-positive pathogens including MRSA and VRE.

Clinical trials

The efficacy and safety of dalbavancin versus vancomycin were evaluated by randomized, controlled, open-label phase 2 study of 75 adults with catheter-related bloodstream infections caused by Gram-positive pathogens [75]. Patients received intravenous dalbavancin (1000 mg stat followed by 500 mg iv 1 week later) or vancomycin (1 g iv bid for up to 14 days). Clinical response was defined as cure or improvement of infection at follow-up visit such that no additional antibiotic treatment was warranted. Overall success rates were 87% (95% CI, 73.2–100.0%) for dalbavancin versus 50% (95% CI, 31.5–68.5%) for vancomycin. Recently, Seltzer et al. [76] conducted a randomized, controlled, open-label trial designed to evaluate the efficacy and safety of dalbavancin in skin and soft-tissue infections (cSSSI) that were known or suspected to be caused by Gram-positive bacteria, including MSSA, MRSA, Group B *Streptococcus* and *S. pyogenes*. A total of 62 patients were randomized to receive a single 1100 mg IV infusion of dalbavancin, a 1000 mg dose of dalbavancin followed by a 500 mg dose administered 1-week later, or a prospectively defined standard-of-care regimen determined by the investigator before randomization. Results from this study demonstrated that clinical success rates were 61.5% for single-dose dalbavancin, 94.1% for two doses of dalbavancin and 76.2% for the standard-of-care regimen. The study showed that two doses of dalbavancin, administered 1-week apart, are effective for the treatment of SSTIs. A randomized, double-blind, controlled study comparing dalbavancin and linezolid has also been conducted in patients with cSSSIs [77]. Both drugs demonstrated comparable efficacy in the clinically evaluable population at the test-of-cure visit (88.9% and 91.2% clinical success rates, respectively). The reported microbiological success rates were comparable at 89.5% (dalbavancin) and 87.5% (linezolid). These findings indicate that dalbavancin is an effective treatment for adults with Gram-positive cSSSIs including those caused by MRSA and two doses of dalbavancin administered 1-week apart were as effective as 14-day twice-daily dosing regimen of linezolid. In addition, in the evaluation of the efficacy of dalbavancin versus either linezolid, cefazolin or vancomycin for the treatment of skin and SSSIs caused by *S. aureus*, the clinical and microbiological success rates of patients who

received dalbavancin were similar to the response rates noted for the comparator agents [71].

Safety profile

Dalbavancin has been found to have a relatively good safety profile and the reported adverse effects include nausea, diarrhoea, constipation, oral candidiasis, pyrexia and hypotension [71]. Laboratory abnormalities including raised liver enzymes and hypokalemia have also been reported.

Other emerging antibiotics

In addition to the five antibiotics reviewed above, there are also a number of other important novel agents being investigated for use in the treatment of infections caused by Gram-positive bacteria. These include telavancin which is a semi-synthetic derivative of vancomycin and ceftobiprole which is a β -lactamase stable cephalosporin with strong affinity for the penicillin binding proteins PBP2a and PBP2x. Telavancin has been shown to be useful in the treatment of cSSSI with cure rates of up to 96%. In several phase 3 trials, the efficacy of ceftobiprole for the treatment of cSSSI was comparable to that of iv vancomycin. Other agents under investigation include doripenem, iclaprim (new diamoniprimidine), ranbezolide (new oxazolidinone) and ceftaroline (new cephalosporin with anti-MRSA and anti-pneumococcal activity).

Conclusion

Daptomycin, tigecycline, linezolid, quinupristin–dalbavancin and dalbavancin are alternative antimicrobial agents useful for the treatment of infections due to drug-resistant Gram-positive cocci. The current body of evidence demonstrates their continued clinical efficacy in the management of these infections. However, as the search for newer antimicrobial agents continues, judicious and responsible usage of these five antibiotics is advocated so as to preserve their continued effectiveness in the management of difficult-to-treat infections caused by Gram-positive pathogens.

Conflict of interest

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